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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/685,432	SHORT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-20 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-20 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed January 26, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-61 were pending. Applicants canceled claims 14, 21 and 27-61 and amended claims 1, 15 and 24. Therefore, claims 1-13, 15-20, 22-26 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections denoted A- are withdrawn in view of applicant's amendments to the claims and/or cancellation of claims. The Double Patenting Rejections are withdrawn in view of Applicants' submitted Terminal Disclaimer. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

5. Claims 1-13, 15-20, 22-26 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claims 1-13, 15-20, 22-26 outline steps for identifying a bioactivity or a biomolecule of interest wherein no distinguishing features are provided for microenvironment (see claim 15), library containing a plurality of clones (see claim 1), mixed population of organisms (see claim 1), oligonucleotide probes (see claim 1), detectable molecule and bioactvity. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the microenvironment, clones, probes, and detectable molecules. This reads on an infinite number of possibilities and thus represents enormous scope. Consequently, there is simply no common attributes that can link together ***all*** of the microenvironments, clones, probes and markers i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of microenvironments, clones, probes and markers that should be screened and thus included in this enormous genus from the few examples provide by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing one example of a library (e.g., see specification, Examples) is insufficient to teach the

entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

With respect to adequate disclosure Applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples*, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat*_(CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. Here, Applicants have not provided enough examples to show that they were in possession of the broad claims.

Furthermore, with regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly*

defined the invention by function of the claimed DNA (encoding insulin)]. Here, the "microenvironment" (see claim 15) is only described by its function i.e., its ability to encapsulate the clones. The Examiner contends that this functional language does not provide the requisite definition "such as by structure, formula [or] chemical name" that is required.

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that a written description rejection should not be applied to method claims (e.g., see 1/26/2004 Response, page 6, last paragraph, "Applicants respectfully submit that the analogy of a method claim to a chemical compound ... is not apt").

[2] Applicants argue that the specification provides a "plethora of specific examples" that adequately describes the invention (e.g., see 1/26/2004 Response, pages 6-8).

This is not found persuasive for the following reasons:

[1] Examiner contends that "method claims" also must be adequately described. (e.g., see Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 228 (W.D.N.Y. 2003); affirmed by the CAFC on appeal, see University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 69 USPQ2d 1886 (Fed.Cir.2004)), wherein the court held that "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the

compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, '[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.'") (emphasis added).

[2] First, the Examiner contends that Applicants have merely provided a "laundry list" of potential examples that are not adequately described (e.g., See, *Fujikawa v. Wattanasin*, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

In addition, the Examiner contends that the species disclosed in the cited references even if assuming arguendo that they were adequately described are not "representative" of the "enormous" scope of the claimed invention. Here, Applicant's claimed scope represents only an *invitation to experiment* regarding possible microenvironment, library clones, mixed population of organisms, oligonucleotide probes, fluorescent markers and bioactvity, which read on an "infinite" number of possibilities. There is simply insufficient disclosure to justify this "enormous" scope. Furthermore, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus, which has not been done.

The Examiner also notes that the claimed invention is highly unpredictable because it reads on an "infinite" number of possibilities. Thus, there is a greater need for representative examples in an unpredictable art that are necessary to demonstrate that applicant had possession

of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. Here, Applicants' specification provides only one working example of a library e.g., Zap-II library (e.g., see Examples in specification) and, as a result, does not meet the "heightened" written description requirement for an unpredictable art area.

Finally, the Examiner notes that an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The Examiner maintains because of the breadth of the claims, the unpredictability of the art and the lack of any working examples, the above standard is not met.

Accordingly, the written description rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 112, second paragraph

7. Claims 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. ***Claim 22*** recites, "the polynucleotide of interest encodes a small molecule" in lines 1-2. The term "small" is a relative term, which renders the claim indefinite and/or

unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b).

Response

8. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

A. Applicants argue that small molecule "does not refer specifically to the size of the molecule" and that those of skill in the art would understand that "small molecule" is simply used to distinguish a chemical molecule or complex, such as a non-proteinaceous enzyme, from molecules containing amino acids or nucleic acids, either of which may be smaller in terms of molecular weight than a large chemical complex (e.g., 1/26/2004 Response, page 9, first paragraph).

This is not found persuasive for the following reasons:

A. The Examiner contends that "small" molecule does refer to the "size" of the molecule and any other interpretation would be repugnant to its usual meaning of the term. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161

F.2d 367, 73 USPQ 482 (CCPA 1947). Furthermore, the Examiner notes that Applicants have not pointed to any specific passage in the specification that supports their position.

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above are hereby maintained.

Claims Rejections - 35 U.S.C. 102

9. Claims 1-10, 13, 15-20 and 22-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Thompson et al (US Patent No. 5,824,485) (Filed **April 24, 1996**).

For ***claim 1***, Thompson et al (see entire document) discloses a method for screening molecular diversity, which anticipates claims 1. For example, Thompson et al discloses [a, c] contacting a library containing a plurality of clones comprising polynucleotides derived from a mixed population of organisms or more than one organism, with at least one oligonucleotide probe labeled with a detectable molecule (e.g., see Thompson et al, column 34, lines 62-65, "The present invention also provides encapsulation as an efficient high-throughput method for growing cells in a confined space"; see also column 35, paragraph 1; see also column 37, line 55; see also column 48, section 5.4.10; see also column 5, lines 38-41, "libraries can be used, the libraries can be further modified to incorporate a reporter regimen tailored to identify clones"; see also column 12, paragraph 3; see also column 27, paragraph 2; see also column 29, paragraph 1; see also column 32, paragraph 1; see also column 33, paragraph 1; see also column 12,

paragraph 2; see especially column 25, paragraph 2, "Either DNA or RNA may be used as starting genetic material for preparing such libraries which may include cDNA libraries, genomic DNA libraries, as well as mixed cDNA/genomic DNA libraries, DNA fragments derived from a plurality of donor organisms, e.g., organisms described in Section 5.1.1, are introduced into a pool of host organisms, such that each host organism in the pool contains a DNA fragment derived from one of the donor organisms"; see also Thompson et al, see section 5.2.3, especially column 37, lines 30-36, "The combinatorial gene expression libraries of the invention may be pre-screened or screened by a variety of methods, including but not limited to, visual inspection, automated image analysis, hybridization to molecular beacon DNA probes (Tyagi et al.1996, *Nature Biotechnol*, 14:303-308) fluorescence activated cell sorting (FACS) and magnetic cell sorting (MACS)"; section also section 5.2; see especially column 32, paragraph 1, "The preselected fragments of DNA contain genes encoding partial or complete biosynthetic pathways, and may be preselected by hybridizing to an initial DNA library a plurality of probes prepared from known genes that may be related to or are involved in producing compounds of interest"; see also column 32, lines 29-56; see also column 34, paragraphs 2-4; see especially column 34, lines 44-47; see also section 5.2.2. disclosing the use of fluorescent probes; see also column 33, line 38; see also column 37, line 35).

Furthermore, Thompson et al. also disclose [b] "normalizing the plurality of polynucleotides" (e.g., see Thompson et al., column 32, lines 14-16, "all the positive clones can be pooled and used for making the biased [i.e., normalized] combinatorial gene expression library. The initial library may be amplified so that DNA donor

organisms can be pre-screened, and DNA from all of the positive clones can be pooled and used for making the biased combinatorial gene expression library"; see also column 32, line 54; see also more generally section 5.1.6; see also column 17, lines 48-62; see especially claims 3, 21; see also column 14, lines 50-51 wherein "slow growing" members were "equalized"; see also column 17, line 36 wherein DNA is "repaired" and thus their numbers are "equalized"; see also column 1, line 35 where "enzymes" are disclosed; see also column 4, line 32; see also column 9, line 14; see also column 10, line 2; see also column 34, line 35; see also column 6, line 55).

Furthermore, Thompson et al discloses [d] separating clones with an analyzer that detects the detectable molecule using probes (see Thompson et al, column 33, line 39 e.g., disclosing the use of "FACS" analysis; see also column 37, line 35; see also column 35, paragraph 2, column 36, paragraph 2; see more generally section 5.2.2.; see also column 47, paragraph 1-7).

For ***claim 2***, Thompson et al discloses [a] contacting the separated clones with a reporter system that identifies a polynucleotide encoding the activity of interest (see Thompson et al, column 5, paragraph 3, "While standard methods of screening gene expression libraries can be used, the libraries can be further modified to incorporate a reporter regimen tailored to identify clones that are expressing the desirable pathways and metabolic products [i.e., polynucleotides encoding the activity of interest]"; see also column 5, lines 55-65; see also abstract; see also figures 7-8, see also column 11, line 33-40).

Furthermore, Thompson et al discloses [b] identifying clones capable of modulating expression or activity of the reporter system thereby identifying a polynucleotide of interest (see Thompson et al, section 5.2.1.; especially column 35, lines 38-67 disclosing reporter constructs with inducible promoters; see also claims 17, 33; see also column 34, line 35; see also column 35, line 66).

For ***claim 3***, Thompson et al discloses an expression library (e.g., see Thompson et al, column 6, paragraph 4; see also column 5, paragraph 4, "standard methods of screening gene expression libraries can be used"; see also figures 1-2; see also column 9, paragraph 4).

For ***claim 4***, Thompson et al discloses a fluorescent molecule (see Thompson et al, column 35, paragraph 2; see also column 36, paragraph 2; see section 5.2.2., especially column 36, last two paragraphs, "A physiological probe as used herein is a fluorescent or colorigenic agent"; see also column 37, paragraphs 1-2).

For ***claim 5***, Thompson et al discloses FACS (see Thompson et al, column 7, line 2; see also figure 9; see also column 33, line 39; see also column 35, line 10).

For ***claim 6***, Thompson et al discloses a mixed population of organisms from an environmental sample (see Thompson et al, column 12, section 5.1.1. Donor Organisms, especially line 43, "Any organism can be a donor organism ... obtained from ... environmental samples").

For ***claim 7***, Thompson et al discloses microorganisms (e.g., see Thompson et al, see column 12, line 59, "the invention is not limited to microorganism donors).

For ***claims 8-9***, Thompson et al discloses extremophiles including thermophiles, acidophiles and halophiles (e.g., see Thompson et al, column 13, last paragraph; see especially column 14, line 2, "The donor organisms may be thermophilic, halophilic, acidophilic, barophilic, methanogenic").

For ***claim 10***, Thompson et al teaches reporter systems that are bioactive substrates (see Thompson et al, column 34, paragraphs 3-4, especially line 45; see especially column 36, last paragraph, "The probe can be an enzyme substrate"; see also column 47, line 28).

For ***claim 13***, Thompson et al discloses (a) obtaining polynucleotides from an population of organisms (see Thompson et al, column 12, lines 38-44, "Any organism can be a donor organism for the purpose of preparing a combinatorial gene expression library of the invention ... from environmental samples [i.e., a mixed population] either cultivable or uncultivable"; see also column 12, line 18). Thompson et al also discloses (b) normalizing the polynucleotides obtained from the sample and (c) generating a library from the normalized polynucleotides (see Thompson et al, column 32, lines 14-16, "all the positive clones can be pooled and used for making the biased [i.e., normalized] combinatorial gene expression library. The initial library may be amplified so that DNA donor organisms can be pre-screened, and DNA from all of the positive clones can be pooled and used for making the biased combinatorial gene expression library"; see also column 32, line 54; see also more generally section 5.1.6; see also column 17, lines 48-62; see especially claims 3, 21).

For ***claims 15-17***, Thompson et al discloses encapsulation via a gel microdrop (e.g., see Thompson et al, column 38, line 15; see also column 38, line 38; see also column 37, line 57).

For ***claims 18-19***, Thompson et al discloses any enzyme and provides several examples including esterase (e.g., see Thompson et al, column 9, line 14; see also column 33, line 35; see also column 34, line 45; see also column 4, paragraph 2).

For ***claim 20***, Thompson et al discloses a detectable label (see Thompson et al, column 34, paragraphs 1-3; see also column 33, line 43).

For ***claim 22***, Thompson et al discloses "small" molecules (see Thompson et al, column 30, paragraphs 6-8; see also column 4, paragraph 2).

For ***claim 23-25***, Thompson et al discloses polynucleotides of interest comprise one or more operons (see Thompson et al, column 25, line 59; see especially column 26, last paragraph; see also column 36, paragraph 1; see most especially claim 9, "The gene expression library of claim 7 in which the cDNA or genomic DNA fragments comprise one or more operons, or portions thereof"). Thompson et al also discloses operons for the polyketide syntheses (see Thompson et al, column 4, paragraph 2; see also column 13, paragraph 4, see also column 32, paragraph 3; see also column 60, paragraph 2; see also column 60, second to lat paragraph). Thompson et al also discloses complete or incomplete metabolic pathways (see Thompson et al, column 32, paragraph 1, "The preselected fragments of DNA contain genes encoding partial or complete biosynthetic pathways, and may be preselected by hybridizing to an initial DNA library a plurality of probes prepared from known genes that may be related to or are involved in producing

compounds of interest"; see also column 6, line 47 providing definition of metabolic pathway; see also figure 1).

For ***claim 26***, Thompson et al discloses FACS (see Thompson et al, column 7, line 2; see also figure 9; see also column 33, line 39; see also column 35, line 10).

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 102(e) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Thompson is silent regarding 'normalizing' polynucleotides, as the term is used in Applicants' specification and claims" and specifically refer to U.S. Patent 6,174,673 in support of this position (e.g., see 1/26/2004 Response, page 10, last paragraph, "Applicants describe 'normalizing' and its advantages as follows in U.S. Patent 6,174,673 ... which is incorporated by reference").

[2] Applicants argue, "Applicants' goal for normalization step is preparation of naturally occurring molecules for equal representation in a screening library ... " (e.g., see 1/26/2004 Response, page 11, paragraph 1).

[3] Applicants argue Thompson does not screen a library that has been "already" normalized (e.g., see 1/26/ 2004 Response, page 11, middle paragraph).

[4] Applicants argue that it is not their purpose to create novel activities or pathways by combinatorial techniques, but rather involves screening "naturally occurring molecules" (e.g., see 1/26/2004 Response, pages 11-12). Applicants also set forth exhibits A-C to support this position and expand on the view that "combinatorial" techniques were not being used (e.g., see attachments).

This is not found persuasive for the following reasons:

[1] First, the Examiner contends that this incorporation is improper because the definition for "normalization" and its associated limitations represents essential subject material. Thus, Applicants would be required to amend the disclosure to include the material incorporated by reference in accordance with MPEP § 608.01(p). The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Second, the Examiner notes that the libraries of Thompson et al. have been "normalized" as outlined by the amended rejection above (e.g., see column 32, lines 14-16). "Normalization" as defined by Webster's II dictionary is "to cause to conform to a norm or standard" (e.g., see Webster's II Dictionary, page 803). Here, the libraries of Thompson were "pre-selected for a specific property [i.e., the standard is the pre-selected specific property]" (e.g., see column 36, line 9; see also column 32, paragraph 1; see also column 32, lines 48-56) and thus Thompson et al. fall within the scope of the term "normalization" because this dictionary definition represents

the broadest reasonable interpretation for the term. Furthermore, this dictionary definition is fully consistent with Applicants' specification because the "specific property" would include amplifying "underrepresented" or "rare" species. For example, the Examiner notes that Thompson et al. do provide methods for "equalizing" slow growing members in a mixed population (e.g., see column 14, lines 50-51; see also column 17, line 36 wherein DNA is "repaired" and thus their numbers are "equalized"). Please note that this dictionary definition has been set forth for the sole purpose of responding to Applicants' arguments.

[2] In response to applicants' arguments that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., "equal representation" in underrepresented clones or providing for clones that have "equal representation") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the Examiner notes that Thompson et al. do provide methods for "equalizing" slow growing members in a mixed population (e.g., see column 14, lines 50-51; see also column 17, line 36 wherein DNA is "repaired" and thus their numbers are "equalized"). Thus, Applicants' assessment that Thompson's biasing achieves an opposite result in factually mistaken.

[3] The Examiner contends that Applicants' arguments are not commensurate in scope with the claims because Applicants' use comprising terminology that does not limit the "order" in which the method steps are to be carried out. See *Interactive Gift Express, Inc. v.*

CompuServe Inc., 231 F.3d 859, 875, 56 USPQ2d 1647, 1661 (Fed. Cir. 2000) ("Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one.").

[4] The Examiner contends that Applicants arguments are not commensurate in scope with the claimed invention. Applicants use "comprising" terminology that would not preclude libraries that have been "rearranged" or "recombined" in a laboratory setting or the use of "combinatorial" procedures as set forth by Exhibits A-C.

Accordingly, the 35 U.S.C. § 102(e) rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

11. Claims 1-13, 15-20, 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al (US Patent No. 5,824,485) (Filed **April 24, 1996**) and Miao et al (Miao, F.; Todd, P.; Kompala, D. S. "A single-cell assay of β-galactosidase in recombinant *E. coli* using flow cytometry" Biotechnology and Bioengineering **(1993)**, 42, 708-715).

For ***claims 1-10, 13, 15-20 and 22-26***, Thompson et al teaches all the limitations stated in the 35 U.S.C. 102(e) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-10, 13, 15-20 and 22-26 and, consequently, also renders obvious claims 1-10, 13, 15-20 and 22-26.

The prior art teaching of Thompson et al differs from the claimed invention as follows:

For ***claims 11-12***, the prior art teachings of Thompson et al differs from the claimed invention by not specifically reciting the use of "C12FDG". Thompson et al implies that C12FDG may be used by reciting the use of β-galactosidase in the reporter system that uses C12FDG i.e., C12FDG is commonly hydrolyzed by β-galactosidase (see Miao below), but the reference does not explicitly state that C12FDG is used.

However, Miao et al teaches the following limitations that are deficient in Thompson et al:

For ***claims 11-12***, Miao et al (see entire document) explicitly teaches the use of "C12FDG" with a "lipophilic group" in assays using β-galactosidase like the one employed by Thompson et al (see Miao et al, abstract; see also page 708, column 2, paragraph 1).

It would have been obvious to one skilled in the art at the time the invention was to use the C12FDG as taught by Miao et al with the β-galactosidase enzyme reporter system as taught by Thompson et al because Miao et al explicitly states that the C12FDG substrate is specifically designed to be used in these types of assays with β-galactosidase. one would have been motivated to use the C12FDG because Miao et al explicitly states that the C12FDG contains a lipophilic group that allows the substrate to penetrate through the cell membrane, which would be advantageous because according to Miao et al, "This improvement provides a great increase in intracellular fluorescence intensity and a reduction in dye transfer among cells. By using this new substrate, it becomes possible to separately count β-galactosidase-positive (plasmid-bearing) and B-galactosidase-negative (plasmid-free) bacterial cells using flow cytometry" (see Miao et al, page 708,

column 2, paragraph 1). One of skill in the art would have been reasonably assured of success because Miao et al shows a successful example using flow cytometry.

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that Thompson does not teach "normalized" libraries and that the secondary references do not compensate for this deficiency (e.g., see 1/26/2004 Response, pages 12-13).

[2] Applicants argue that their invention is drawn to gene clusters or pathways of genes as found in nature, "without manipulation" (e.g., see 1/26/2004 Response, page 13, last paragraph) and thus is distinguished from the prior art.

[3] Applicants argue that the prior art references do not "increase the chances that an activity encoded by a rare organism in the sample will be as likely to be discovered in the screening [process] as that of an organism whose presence predominates in the sample" (e.g., see 1/26/2004 Response, page 14, paragraph 2).

[4] Applicants argue that there is no reasonable expectation of success because "neither Thompson nor Miao discusses any technique by which a diverse library can be adjusted to provide equal representation of the polynucleotides from rare members" (e.g., see 1/26/2004 Response, page 15, paragraph 1).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Thompson does teach normalized libraries and, as a result, Applicants' arguments are moot (e.g., see 35 U.S.C. § 102 rejection/response, which is incorporated in its entirety herein by reference).

[2] The Examiner contends that Applicants' arguments are not commensurate in scope to the claims because Applicants' use of "comprising" terminology would not preclude the possibility of "manipulating" the genes.

[3-4] In response to applicants' arguments that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., "increase the chances" of underrepresented clones; "adjusted to provide equal representation") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the Examiner notes that Thompson et al. do provide methods for "equalizing" slow growing members in a mixed population (e.g., see column 14, lines 50-51; see also column 17, line 36 wherein DNA is "repaired" and thus their numbers are "equalized"). Thus, Applicants' assessment that Thompson's biasing achieves an opposite result in factually mistaken.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
April 21, 2004

BENNETT CELSA
PRIMARY EXAMINER